REMARKS

Claims 1-5, 14-20, 29, and 34-36 were pending in this application.

Restriction to one of the following three invention groups has been required under 35 U.S.C. § 121:

Group I: Claims 1-5, 14-20, and 29 directed to antibodies and a hybridoma;

Group II: Claim 34, directed to a method for producing polyclonal antibodies;

Group III: Claims 35 and 36, directed to a method for producing a monoclonal antibody.

Applicants affirm the provisional election of Group 1. Claims 34-36, drawn to non-elected subject matter, have been canceled without prejudice to Applicants' rights to pursue the subject mater of the canceled claims in related applications. Claim 20 has been amended to clarify the relationship of the subject matter claimed to that recited in Claim 19. This amendment in no way narrows the scope of the subject matter recited in amended Claim 20.

Claims 1-5, 14-20 and 29, therefore, are currently pending. A marked-up copy of the amended claims is attached hereto as Exhibit 3. A clean copy of the pending claims is attached hereto as Exhibit 4.

The specification has been amended to include appropriate sequence identifiers (SEQ ID NOS), and to reflect the fact that the hybridomas deposited in connection with the application have been deposited under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. A marked-up copy of the paragraphs of the specification that have been amended is attached hereto as Exhibit 1. A clean copy of the amended paragraphs is attached hereto as Exhibit 2.

Submitted herewith is a Sequence Listing in paper form, accompanied by a Response to Notice to Comply including statement regarding the Sequence Listing. Briefly, the statement specifies that the Sequence Listing submitted herewith is identical to the Sequence Listing submitted in parent application Serial No. 09/232,532, and authorizes use of the computer readable form of the Sequence Listing from application Serial No. 09/232,532 in the instant application. As such, Applicants estimate that the instant application fully complies with the rules set forth in 37 C.F.R. §§ 1.821-1.825.

Entry of the amendments and remarks contained herein is respectfully requested.

1. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn.

Claims 1-5, 14-20, and 29 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite in view of the use of the term "immunologically reacts with." This rejection should be withdrawn for the reasons presented below.

35 U.S.C. § 112, second paragraph, states that the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. According to the Federal Circuit, the "distinctly claiming" requirement means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. *See Miles Laboratories, Inc. v. Shandon Inc.*, 27 USPQ2d 1123, 1125-26 (Fed. Cir. 1993). The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *See id.* If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, 35 U.S.C. § 112 demands no more. *See id.*

The Office Action does not provide any sustainable basis for rejecting the present claims under 35 U.S.C. § 112, second paragraph. Applicants submit, first, that the terms "immunologically" and "reacts with" have acquired a standard meaning in the art. In addition, representative assays for measuring immunological reactivity are provided in the instant specification. See, *e.g.*, p. 7, ll. 14-25, of the instant specification. Furthermore, the Board of Patent Appeals and Interferences has held that the recitation of the term "reacting" in a claim is not indefinite. See *Ex parte Biel*, 137 USPQ 315, 317 (Bd. Pat. App. & Int. 1962). The claims of the present application, read in view of the specification, therefore, clearly apprise those skilled in the art of scope of the subject matter of Applicants' invention.

Claim 20 is rejected as lacking antecedent basis. Without acquiescing to the propriety of the rejection, Claim 20 has been amended to clarify its relationship to the antibody of claim 19. This amendment in no way narrows the scope of the claimed subject matter.

Applicants respectfully submit that Claims 1-5, 14-20, and 29 are sufficiently definite to satisfy the requirements of 35 U.S.C. § 112, second paragraph. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-5, 14-20, and 29 under 35 U.S.C. § 112, second paragraph.

2. The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn.

Claims 1-5, 14-20 and 29 are rejected under 35 U.S.C. § 102(b) as anticipated by Presky *et al.* ("Presky") as evidenced by Gately *et al.* ("Gately") and by "admissions" in instant specification Figure 4. Claims 1-4, 14-17 and 19 are rejected under 35 U.S.C. § 102(b) as anticipated by Cytokine Bulletin. Claims 1-4 and 29 are rejected under 35 U.S.C. § 102(b) as anticipated by Trinchieri *et al.* ("Trinchieri") as evidenced by Gately and Carter *et al.* ("Carter"). These rejections should be withdrawn for the reasons set forth below.

Presky Does Not Anticipate Any of the Claims

The only anti-IL-12 antibody used in Presky is referred to as 20C2. The 20C2 antibody is a rat monoclonal antibody (*see* Gately, col. 44, ll. 42-45 for verification), that is reported to be specific for the human IL-12 heterodimer made up of a p35 and a p40 subunit. Contrary to the Examiner's contention, Presky does not teach both polyclonal and monoclonal antibodies to the human IL-12 p75 heterodimer, nor does Presky teach that such antibodies can be humanized or used as therapeutic drugs. Further, because the 20C2 antibody is a *rat* monoclonal antibody, it was not produced from a mouse cell line.

The standard for anticipation under 35 U.S.C. § 102 is strict identity. Anticipation under § 102 can only be established by a single prior art reference that teaches each and every element of the claimed invention. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 223 USPQ 1264 (Fed. Cir. 1984).

The antibodies recited in Claims 1-4 are produced from a mouse or a mouse cell line, *i.e.*, the compositions are *mouse* antibodies. Dependent Claim 5 further recites an antibody that has been humanized. Claim 29 recites a mouse hybridoma. In contrast, as pointed out above, the 20C2 antibody is a non-humanized *rat* antibody. Thus, the claimed compositions clearly differ from the antibody described in Presky. As such, Presky cannot anticipate Claims 1-5.

Claims 14-20 recite monoclonal antibodies to human IL-12 heterodimer, wherein the antibodies are not immunologically reactive with any epitope presented by the human IL-12 p40 subunit and neutralize at least about 90% of the bioactivity of human IL-12.

As discussed above, Presky teaches the 20C2 antibody. The experiments presented in Presky were designed to study two human IL-12 binding proteins, referred to in Presky as human IL-12Rβ1 and human IL-12Rβ2. Presky states that IL-12Rβ1 binds human IL-12 with low affinity (K_D of about 10 nM) and IL-12Rβ2 binds human IL-12 with a K_D of about 5 nM. Presky

further states when IL-12Rβ1 and IL-12Rβ2 are co-expressed in COS-7 cells, a high affinity (K_D of about 50 pM) binding site also appears. Presky reports that the 20C2 antibody blocks IL-12 binding to IL-12Rβ2 but not IL-12 binding to IL-12Rβ1 (Presky Fig. 2, and Summary, p. 392).

The Examiner contends that because Presky reports that 20C2 blocks binding of human IL-12 to IL-12Rβ2, this must mean that 20C2 neutralizes at least about 90% of the bioactivity of human IL-12. Applicants respectfully point out that this contention is in error, as evidenced by Presky *et al.* ("Presky 1998"),[1/] attached hereto as Exhibit 5.

The experiments presented in Presky 1998 are also directed toward the study of human IL-12 binding to IL-12Rβ1 and IL-12Rβ2. As in Presky, the results in Presky 1998 also report that the 20C2 antibody blocks human IL-12 binding to IL-12Rβ2, but Presky 1998 also reports, however, that the 20C2 antibody actually *increases* human IL-12 binding to IL-12Rβ1 (Fig. 3 and pp. 2175-2176). Further, the results summarized in Figures 5 and 6 clearly demonstrate that the 20C2 antibody *fails* to neutralize at least about 90% of the bioactivity of human IL-12.

The experiment summarized in Figure 5 tested, *inter alia*, the effect of the 20C2 antibody on IL-12-stimulated proliferation of PHA-activated lymphoblasts. The experiment demonstrates that even at the highest concentration tested, administration of 20C2 antibody alone fails to inhibit at least about 90% of IL-12 induced proliferation (Fig. 5A, closed squares). Only when coadministered with either another antibody (Fig. 5A, open circles) or a peptide inhibitor (Fig. 5B, open circles) does the amount of inhibition approach this level.[2/]

[1/] Presky, D. *et al.*, "Analysis of the Multiple Interactions Between IL-12 and the High Affinity IL-12 Receptor Complex," Journal of Immunology, Vol. 160, pages 2174-2179 (1998).

[2/] In Presky 1998 Figs. 5A and 5B, the lower horizontal dotted line represents the control level of PHA-activated proliferation that occurs in the absence of IL-12, and the upper horizontal dotted line represents the control level of IL-12-induced proliferation. The amount of inhibition, therefore, can be calculated relative to these two control values.

The experiment summarized in Figure 6 tested, *inter alia*, the effect of the 20C2 antibody on IL-12-stimulated interferon-gamma (IFN-γ) production by human peripheral blood mononuclear cells (PBMC). The experiment demonstrates that administration of 20C2 antibody alone at either concentration tested has no effect on IFN-γ production. Only when coadministered with either a peptide inhibitor (Fig. 6A) or another antibody (Fig. 6B) is significant IFN-γ inhibition observed.

The instant specification itself provides further corroboration that the 20C2 antibody does not neutralize at least about 90% of human IL-12 bioactivity. *See, e.g.*, p. 2, l. 24, to p. 3, l. 2; Example 12, pp. 27-28, especially p. 27, ll. 19-21, and Figure 3; and Example 14, pp. 29-30, especially p. 30, ll. 1-4, and Figure 5.

The 20C2 antibody, therefore, clearly fails to neutralize at least about 90% of the bioactivity of human IL-12. As such, Presky cannot, therefore, anticipate Claims 14-20.

Cytokine Bulletin Does Not Anticipate Any of the Claims

Claims 1-4, 14-17 and 19 are rejected under 35 U.S.C. § 102(b) as anticipated by Cytokine Bulletin. This rejection should be withdrawn for the reasons presented below.

The Examiner contends that Cytokine Bulletin (R&D Systems) discloses an IL-12 heterodimer-specific monoclonal antibody that neutralizes human IL-12 bioactivity. Applicants respectfully point out that this contention is in error. Cytokine Bulletin describes an ELISA-based kit for quantitation of human IL-12 heterodimer. The immobilized antibody used in this ELISA kit is reported to be specific for IL-12 heterodimer, but nothing in Cytokine Bulletin indicates that the immobilized antibody exhibits any neutralizing activity whatsoever. The antibody described in Cytokine Bulletin that reportedly exhibits IL-12 neutralizing activity is actually a *second*, completely separate antibody (R&D Systems Catalog number AB-219-NA) that was used to verify the quantitation results obtained from the ELISA kit.

Attached hereto as Exhibit 6 is the R&D Systems technical literature regarding the AB-219-NA antibody, which demonstrates that the antibody, while reportedly exhibiting neutralizing activity, cannot anticipate any of Claims 1-4, 14-17 or 19. The R&D Systems technical literature reveals that the neutralizing antibody is actually a *polyclonal* mixture of total *goat* IgG antibodies. As discussed above, the antibodies of Claims 1-4 are *mouse* antibodies, and the antibodies of Claims 14-17 and 19 are *monoclonal* antibodies.

As stated above, the standard for anticipation under 35 U.S.C. §102 is strict identity, and anticipation under § 102 can only be established by a single prior art reference that teaches each and every element of the claimed invention. *Structural Rubber Products, supra*, 223 USPQ 1264. Clearly, therefore, Cytokine Bulletin cannot anticipate Claims 1-4, 14-17, or 19.

Trinchieri Does Not Anticipate Any of the Claims

Claims 1-4 and 29 are rejected under 35 U.S.C. § 102(b) as anticipated by Trinchieri *et al.* ("Trinchieri") as evidenced by Gately and Carter *et al.* ("Carter"). This rejection should be withdrawn for the reasons presented below.

As discussed above, the antibodies recited in Claims 1-4 (and produced by the hybridoma recited in claim 29) immunologically react with the human IL-12 heterodimer but do not immunologically react with human IL-12 p40 subunit. The teaching provided in Trinchieri fails to either describe such antibodies or provide teaching that would enable one of skill in the art to make such antibodies without undue experimentation.

The Examiner points to Trinchieri Claims 1, 3, 4, 5 and 7 and Figures 1 and 2 to support the contention that Trinchieri anticipates Claims 1-4 and 29 of the instant application. Nothing in Claims 1, 4, 5, or 7 describe or teach anti-IL-12 antibodies that are specific for the human IL-12 heterodimer while not reacting with an epitope of the p40 subunit. Dependent Claim 3 recites an antibody that reacts with IL-12 heterodimer and reacts with the 30-35 KD IL-12 subunit. While

nothing in the Trinchieri patent is inconsistent with the presently claimed subject matter, this is not enough to anticipate the claims. *See Rowe v. Dror*, 42 USPQ2d 1550, 1555 (Fed. Cir. 1997), in which, although third party's patent did not explicitly describe anything inconsistent with subject matter recited in appellant's patent claims, this did not suffice to show anticipation.

For the reasons set forth above, the rejections under 35 U.S.C. § 102 should be withdrawn.

3. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn.

Claims 1, 5, 14, 18 and 20 are rejected under 35 U.S.C. § 103(a) as obvious over Cytokine Bulletin in view of Bendig and "admissions" at instant specification page 16. Claims 1, 5, 14, 18 and 20 are rejected under 35 U.S.C. § 103(a) as obvious over Trinchieri in view of Gately and Bendig and "admissions" at instant specification page 16. Claim 29 is rejected under 35 USC 103(a) as obvious over Cytokine Bulletin in view of EP 0677533 ("EP '533"). These rejections should be withdrawn for the reasons presented below.

The deficiencies in the teaching presented in Cytokine Bulletin and in Trinchieri are discussed in detail, above. Neither the addition of Bendig nor that of EP '533 cure these deficiencies. In particular, the Examiner uses Bendig to show that reliable methods for humanization of antibodies were known in the art at the time the instant application was filed. As discussed in detail above, however, antibodies of either Cytokine Bulletin or Trinchieri differ from the claimed antibodies in ways other than the fact that the Cytokine Bulletin and Trinchieri antibodies are not humanized. In order to render the invention obvious, a combination of prior art references must teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). Because the combinations of either Cytokine Bulletin or

Trinchieri with Bendig fail to teach the claimed antibodies, these combinations cannot render Claims 1, 5, 14, 18, or 20 obvious.

The Examiner apparently uses EP '533 to show that methods for generating hybridomas that produce monoclonal antibodies were known at the time the instant application was filed. As discussed in detail, above, however, the antibodies produced by the hybridomas recited in Claim 29 differ from the antibodies of Cytokine Bulletin. but not much though Merely combining the teaching of Cytokine Bulletin with that of EP '533, therefore, does not teach the hybridomas of Claim 29. As such, the combination of Cytokine Bulletin and EP '533 does not render Claim 29 obvious. *Id.*

For the reasons set forth herein, the rejection of Claims 1, 5, 14, 18, 20, and 29 under 35 U.S.C. § 103(a) should be withdrawn.

4. **The Double Patenting Rejection** MAINTAIN

Claims 1, 5, 14-20 and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-23 of U.S. Patent No. 6,225,117. While not acquiescing as to the propriety of the rejection, and in view of the fact that the final form of allowable claims may yet remain to be agreed upon, Applicants respectfully defer addressing this rejection until such time as the claims are found to be allowable but for this remaining issue.

CONCLUSION

In view of the preceding remarks, Applicants submit that this application is in condition for allowance. Applicants respectfully request reconsideration and withdrawal of each ground of rejection set forth in the May 9, 2001 Office Action and earnestly solicit favorable action on all pending claims.

Respectfully submitted,

Dated: November 9, 2001

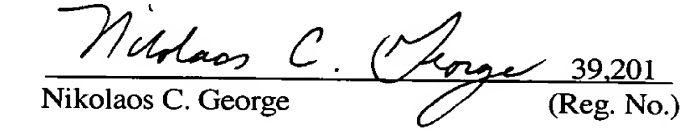

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EXHIBIT 1
MARKED UP COPY OF SPECIFICATION PARAGRAPHS THAT HAVE BEEN AMENDED:

On page 6, the paragraph beginning "Fig. 6 is a nucleotide sequence encoding a portion of the heavy chain..." has been amended as follows:

Fig. 6 is a nucleotide sequence (SEQ ID NO: 1) encoding a portion of the heavy chain variable region of the p75 heterodimer specific 16G2 antibody, and the amino acid sequence (SEQ ID NO: 2) deduced from this nucleotide sequence.

On page 6, the paragraph beginning "Fig. 7 is a nucleotide sequence encoding a portion of the heavy chain variable region..." has been amended as follows:

Fig. 7 is a nucleotide sequence (SEQ ID NO: 3) encoding a portion of the heavy chain variable region of the p75 heterodimer specific 20E11 antibody, and the amino acid sequence (SEQ ID NO: 4) deduced from this nucleotide sequence.

On page 14, the paragraph beginning "In particular, the present invention provides four antibodies, 5F2, ..." has been amended as follows:

In particular, the present invention provides four antibodies, 5F2, 16F2, 16G2 and 20E11 to the p75 heterodimer of human IL-12 which are produced by hybridomas having ATCC designation numbers HB-12446, HB-12447, HB-12449, and HB-12448, respectively. These hybridomas were deposited on December 11, 1997, with the ATCC (American Type Culture Collection), 10801 University Boulevard, Manassas, Virginia 20110-2209, under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, and comply with the criteria set forth in 37 C.F.R. § 1.801-1.809 regarding availability and permanency of deposits. However, the present invention is not limited to these four antibodies. Any antibodies having the characteristics described herein are encompassed.

On page 14, the paragraph beginning "Fig. 6 provides the nucleotide sequence encoding a portion of the heavy chain variable region..." has been amended as follows:

Fig. 6 provides the nucleotide sequence (SEQ ID NO: 1) encoding a portion of the heavy chain variable region of the p75 heterodimer specific 16G2 antibody and the amino

acid sequence (SEQ ID NO: 2) deduced from this nucleotide sequence. The nucleotide sequence (SEQ ID NO: 3) encoding a portion of the heavy chain variable region of the p75 heterodimer specific 20E11 antibody and the amino acid sequence (SEQ ID NO: 4) deduced from this nucleotide sequence (SEQ ID NO: 3) is provided in Fig. 7. It will be understood by those skilled in the art that conservative amino acid changes can be made in the constant regions of the heterodimer specific IL-12 antibodies herein without significantly affecting the antigen binding specificity/affinity. Heterodimer specific IL-12 antibodies containing amino acid changes in the variable framework regions or complementary determining regions can be expected to have a greater effect on antigen binding specificity/affinity.

On page 31, the paragraph beginning "The nucleotide sequences of a portion of the variable region of the immunoglobulin..." has been amended as follows:

The nucleotide sequences of a portion of the variable region of the immunoglobulin heavy chain gene encompassing framework region (FR) 1, complementarity determining region (CDR) 1, FR2, CDR2, FR3, CDR3, and FR4 of IL-12 antibodies produced by hybridoma cell lines HIL-12F3-16G2 and HIL-12F3-20E11 and the deduced amino acid sequences thereof are shown in Fig. 6 (SEQ ID NO: 1), (SEQ ID NO: 2) and Fig. 7, (SEQ ID NO: 3), (SEQ ID NO: 4), respectively. The CDR sequences are underlined. Comparison of available sequence information showed that the heavy chains of antibodies produced by hybridomas HIL-12F3-16G2 and HIL-12F3-20E11 exhibit 94% homology at the DNA level and 93% similarity at the amino acid level.